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Research progress of sphingosine 1-phosphate receptor 3 in the cardiovascular system

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Highlights

- Sphingosine 1-phosphate receptor 3 (S1PR3) promotes the proliferation of vascular endothelial cells and enhances barrier function.
- S1PR3 is a promising target for clinical treatment of cardiac ischemia-reperfusion, cardiac fibrosis and atherosclerosis.
- Fingolimod and other modulators of S1PR3 have shown therapeutic efficacy in phase I and II clinical trials for cardiovascular diseases.
- S1PR3 play crucial roles in the perioperative evaluation and treatment of the cardiovascular system, as well as in sepsis.

Abstract

Sphingosine 1-phosphate receptor 3 (S1PR3) is one of the five receptors of sphingosine 1-phosphate, actively participating in physiological processes such as angiogenesis and endothelial cell differentiation. Widely expressed in various tissue cells such as muscle cells, immune cells, lymphocytes, endothelial cells, and fibroblasts, S1PR3 has garnered increasing attention in research, showcasing its involvement in various pathophysiological processes and its important role in the body's inflammatory and immune responses. In the cardiovascular system, S1PR3 is involved in many pathophysiological processes, including angiogenesis, maintaining vascular permeability, lymphocyte transport, and physiological function of the heart. Moreover, it also plays a regulatory role in the treatment of cardiovascular diseases, such as heart ischemia/reperfusion, atherosclerosis, and cardiac fibrosis. S1PR3 also plays a crucial role in evaluation and treatment during the cardiovascular system in perioperative period and has a powerful therapeutic effect in sepsis. Regulators related to S1PR3 exhibit therapeutic potential in clinical treatments of cardiovascular diseases. This article aims to explore the role and research progress of S1PR3 in the cardiovascular system.

Keywords: Sphingosine 1-phosphate, sphingosine 1-phosphate receptor 3, cardiovascular system

Introduction

Sphingosine 1-phosphate (S1P) serves a pivotal signaling lipid in cell membrane metabolism and synthesis, which is generated by phosphorylation of sphingosine kinase-1 (SPHK1) or sphingosine kinase-2 (SPHK2) in plasma [1]. S1P can also participate in regulating multiple physiological and pathological processes in the body, including cell proliferation and survival, maturation, aging, and death [2]. S1P can bind to five G protein coupled receptors and act as the main endogenous agonist of the sphingosine-1-phosphate receptor 3 (S1PR3). This interaction plays a significant role in physiological and pathological processes such as cell pro-

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liferation and migration, ischemia-reperfusion, inflammation, tumor invasion and migration, vascular tension, and tissue fibrosis.

Recent investigations have been delving into the potential of KRX-725, an antagonist targeting S1PR3. KRX-725 bears significant clinical relevance as a therapeutic agent against inflammation-related fibrotic responses, with potential applications extending to the treatment of myocardial ischemia, tissue transplantation or peripheral blood vessels [3, 4]. S1PR3 also plays a crucial role in evaluation and treatment during the cardiovascular system in perioperative period and has a powerful therapeutic effect in sepsis. Simultaneously, the emerging recognition of S1PR3 in the cardiovascular system not only indicates the research direction of S1PR3, but also underscores the clinical significance of S1PR3 in the prevention and treatment of cardiovascular diseases.

Structure and function of S1P and S1PR3

Structure and function of S1P

Sphingosine 1-phosphate (S1P) operates as a crucial sphingolipid involved in ceramide synthesis within the endoplasmic reticulum. Under the catalysis of serine palmitoyltransferase, it combines serine and palmitoyl-CoA to generate ceramides [5]. Additionally, ceramides can undergo hydrolysis via sphingomyelinases, swiftly deacylated by ceramidases to yield sphingosine [5]. Subsequently, sphingosine is phosphorylated by SPHK1 or SPHK2, ultimately forming S1P [6]. In cellular homeostasis maintenance, S1P may undergo phosphorylation mediated by phosphatases, yielding sphingosine [7]. Degradation pathways for S1P involve three enzymes: S1P phosphatase, S1P lyase and lipid phosphate phosphohydrolase. S1P lyase cleavage predominantly results in the irreversible generation of 1-phosphate ethanolamine and hexaenal in most cells [8].

Cells excrete S1P from the cytoplasm through paracrine or autocrine pathways. Hydrophobic S1P traverses the cell membrane by transport carrier, subsequently binding to chaperone proteins after extrication, and circulating within the bloodstream by associating with serum albumin and high-density lipoprotein (HDL) [6]. Despite its relatively low expression levels within cells or interstitial fluid, S1P is abundant in lymph and blood, establishing a notable gradient discrepancy [5]. This gradient plays a pivotal role in lymphocyte trafficking, facilitating efficient egress from lymphoid organs. Mature T cells, for instance, rely on precise S1P gradients for departure from the thymus; disruption of this gradient impedes their egress. Moreover, the S1P gradient influences the trafficking of natural killer cells, B cells, and dendritic cells [9].

The equilibrium of S1P concentration is jointly regulated by SPHK1 and SPHK2, ensuring its stability within cellular environments.

Structure and function of S1PR3

S1P binds to S1P receptors (S1PRs) to exert its diverse biological functions. S1PRs are G protein-coupled receptors with five isoforms of S1PR1-5, expressed in various tissues of the body [10]. The structure framework of S1PR3 shows the canonical seven-transmembrane bundles holding the unbent d18:1 S1P. Notably, it features an extracellular lid consisting of the N-terminal helix, extracellular loop 2, and extracellular loop 3. The N-terminal region forms a helical cap and contributes to ligand interaction, while disulfide bonds are established within extracellular loop 2 (Cys178-Cys185) and extracellular loop 3 (Cys269-Cys274) [11].

S1PRs are highly expressed across multiple tissue cell types, e.g., S1PR1, S1PR2, and S1PR3 in blood vessels; S1PR1 and S1PR3 in endothelial cells (ECs); and S1PR2 and S1PR3 in vascular smooth muscle cells (VSMCs) [12, 13]. Besides, S1PR3 mediates S1P signaling in myocardial fibroblasts [14]. Within endothelial cells, S1PR3 may contribute to nitric oxide (NO)-mediated vasodilation, while in vascular smooth muscle cells, it participates in Rho-mediated vasoconstriction [15, 16]. Activation of S1PR3 has been associated with effects on heart rate and the risk of atrioventricular blocks [17]. Furthermore, S1PR3 activation triggers the generation of reactive oxygen species (ROS) via nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2) under the influence of the class III phosphatidylinositol 3-kinase complex. This activation promotes phagosome maturation during sepsis, enhancing macrophage bacterial engulfment [18]. Upon LPS induced lung injury, S1PR3 detachment from endothelial cells disrupts endothelial barrier function. Mice lacking S1PR3 or treated with specific antagonists have demonstrated protection against LPS-induced fatal sepsis [19]. Studies have found that S1PR3 is an important molecule in the fibrosis process, where inhibiting S1PR3 can attenuate fibrosis by impeding epithelial-mesenchymal transition through the S1PR3/SMAD2/3 pathway [20]. S1PR3 can be coupled with Gq/11, Gi/o and G12/13 to regulate immune responses, mediating P-selectin-dependent leukocyte rolling through S1PR3

Table 1. Related pathways in this review

Pathway	Influence
S1P→S1PR3→PI3K/Akt [24]	Promoti the proliferation of EPCs
S1P→S1PR3/PDGFR-β/Akt [40]	Promoting migration and angiogenesis of endothelial progenitor cells
S1P→S1PR3/RhoA/ROCK [29]	Promoting endothelial cell permeability, enhancing barrier action
S1PR3-Ga12/13→RhoA, PKD [27]	Cardio-protection
S1PR2-S1PR3→Cx43-S368 [30]	Preventing cell-to-cell transmission of death signals
HDL-S1P→S1PR3-Gi protein→Rho/ROCK,PI3K/Akt,p38MAPK [34, 35]	Promoting EC migration and inhibiting atherosclerosis
HDL-S1P→S1PR3/STAT3/Survivin [36]	Inhibiting macrophage recruitment induced apoptosis
S1P/S1PR3/TGF-β/Smad3 [39]	Inhibiting cardiac fibrosis
S1PR3→Rho GTPases→ROS [39]	Ameliorating of cardiac fibrosis
S1P/S1PR3→SUR2/Kir6.1 [41]	Promoting the transportation of fibroblasts

Note: S1P, sphingosine 1-phosphate; S1PR, S1P receptor; PI3K, phosphatidylinositol-3 kinase; Akt, protein kinase B; EPC, endothelial progenitor cell; PDGFR-β, platelet-derived growth factor beta; ROCK, Rho and Rho kinase; PKD, protein kinase D; CX43-S368, connexin 43 at S368; HDL, high-density lipoprotein; MAPK, mitogen activated protein kinase; EC, endothelial cell; STAT3, Germline signal transducer and activator of transcription 3; TGF-β, Transforming growth factor beta; Smad-3, drosophila mothers against decapentaplegic protein 3; ROS, reactive oxygen species; SUR2, sulfonylurea receptor 2; Kir6.1, pore-forming subunit of K-ATP channel.

and Gq/11 coupling [21]. Additionally, reports suggest that S1P induces cyclooxygenase-2 expression and prostaglandin E2 production in human granulosa cells through the YAP signaling pathway mediated by S1PR1/S1PR3 [22].

S1PR3 and signaling pathway

S1PR3 exerts its influence on various physiological and pathological processes of the body through signaling pathways. S1PR3 functions by mediating the mitogen activated protein kinase (MAPK) and PI3K-Akt (phosphatidylinositol-3 kinase/serine threonine kinase) pathways, activating downstream Ras/extracellular signal-regulated kinase 1/2 and other downstream pathways. Research indicates that S1PR3-mediated PI3K-Akt pathway activation can ameliorate blood-brain barrier damage and stimulate endothelial progenitor cell (EPC) proliferation [23, 24]. Moreover, S1PR3 participates in the feedback loop, where the S1P-S1PR1/S1PR3-YAP (Yes-associated protein 1) pathway c has been implicated in lymphoma development and tumor invasion (**Figure 1**) [25]. ECs leverage the S1P-S1PR1/S1PR3 pathway to facilitate vascular relaxation [26]. In myocardial cells, S1PR3 can activate RhoA, Protein kinase D, and mitigate cellular damage [27]. S1PR3's activation also influences neural processes, contracting them rapidly through Rho and Rho kinase (ROCK) pathways, phosphorylating Collapse response regulatory protein 2, and modulating EC permeability [28, 29]. VSMCs contract blood vessels under the mediation of the S1P-S1PR2/S1PR3 pathway, which also regulates myocardial cell death and alleviates myocardial ischemia-reperfusion injury [26, 30]. Furthermore, S1PR3 can activate endothelial NO synthase in an NO - dependent pathway in ECs, leading to NO production and subsequent vascular relaxation [31]. HDL promotes angiogenesis by regulating S1P-S1PR3, protects against myocardial ischemia-reperfusion injury, migrates vascular ECs, inhibits atherosclerosis and macrophage-induced apoptosis [32-36]. The absence of S1PR3 can reduce the recruitment of monocytes/macrophages, increase the content of smooth muscle cells in the lesion site, and reduce the area of cardiac fibrosis [37-39]. Moreover, S1P can regulate endothelial progenitor cell migration and angiogenesis through the S1PR3/PDGFR-β (Platelet-derived growth factor beta)/Akt signaling pathway [40]. Additionally, it can modulate the S1PR3/TGF-β (Transforming growth factor

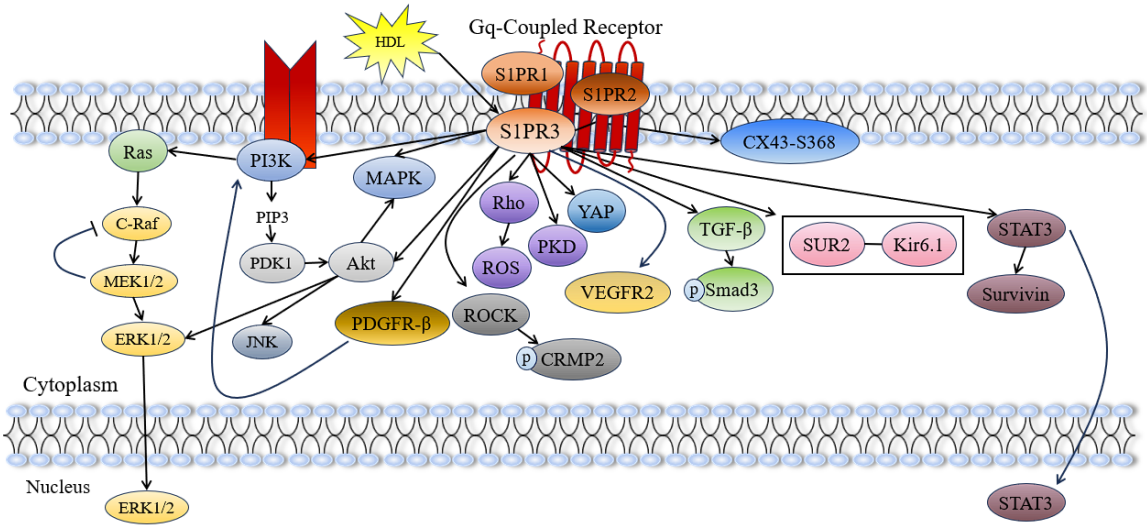

Figure 1. S1PR3 and signaling path. S1PR, sphingosine 1-phosphate receptor; Ras, rat sarcoma; C-Raf, C-Raf kinases; MEK1/2, mitogen-activated protein kinase kinases 1/2; ERK1/2, extracellular signal-regulated kinase1/2; PI3K, phosphatidylinositol-3 kinase; PDK1, 3-phosphoinositide-dependent protein kinase 1; JNK, c-Jun N-terminal kinase; HDL, high-density lipoprotein; MAPK, mitogen activated protein kinase; Akt, protein kinase B; PDGFR-β, Platelet-derived growth factor beta; ROS, Reactive oxygen species; ROCK, Rho and Rho kinase; YAP, Yes-associated protein 1; PKD, protein kinase D; CRMP2, collapse response regulatory protein 2; VEGFR2, vascular endothelial growth factor receptor-2; TGF-β, transforming growth factor beta; Smad-3, drosophila mothers against decapentaplegic protein 3; CX43-S368, connexin 43 at S368; SUR2k, sulfonylurea receptor 2; Kir6.1, pore-forming subunit of K-ATP channel; STAT3, germline signal transducer and activator of transcription 3.

beta)/Smad3 pathway, influencing cardiac fibrosis, and regulate the SUR2 (Sulfonylurea receptor 2)/Kir6.1 (Pore-forming subunit of K-ATP channel) pathway to promote fibroblast transport [39, 41]. S1PR3 activation also triggers Rho GTP enzyme activation, promotes ROS production, and contributes to myocardial fibrosis (**Table 1** and **Figure 1**) [39].

Effects of S1PR3 on the cardiovascular system

The cardiovascular system consists of two essential components: the heart and blood vessels, and the mortality rate of cardiovascular disease is extremely high. S1PR3 is expressed in a variety of cells of the cardiovascular system, such as ECs, VSMCs, cardiac fibroblasts, and cardiomyocytes [6].

Effect of S1PR3 on vascular ECs and barrier action

Under external stimuli, S1P can regulate vascular relaxation levels, EC permeability, and affect barrier effects through S1PR3.

Vascular maturation relies on the proliferation of vascular smooth muscle cells, pericytes and EC regeneration. S1P-regulated EDG signaling is instrumental in vascular EC neogenesis and VSMC recruitment. ECs promote vascular relaxation mediated by S1P-S1PR1/S1PR3 signaling, and VSMCs constrict blood vessels mediated by S1P-S1PR2/S1PR3 [26]. S1PR3 activation triggers the NO-dependent pathway, leading to nitric oxide synthase activation in ECs, NO production, and subsequent diffusion to VSMCs, inhibiting cell contraction and inducing vasorelaxation [31]. Furthermore, S1PR3 is closely related to the activity of EPCs. S1P activates S1PR3 and the downstream pathway PI3K/Akt to promote the proliferation of EPCs [24]. HDL upregulates the expression of vascular endothelial growth factor (VEGFR2) via S1PR3, fostering angiogenesis. The S1P-S1PR3-VEGFR2 signaling pathway holds significant implications for vascular remodeling in cardiovascular disease [32].

Moreover, research highlights the role of S1P in inducing migration and angiogenesis of EPCs through the S1PR3/PDGFR-β/Akt signaling pathway [40]. S1P activation of the S1PR3-RhoA-ROCK pathway enhances EC permeability and reinforces barrier action [29]. In acute lung injury, S1PR3 overexpression in plasma correlates with EC dysfunction, suggesting its potential as a novel acute lung injury marker [42]. Research has shown that FTY720 (fingolimod) may serve as a functional antagonist of S1PR3 to maintain a balance between angiogenesis and microvascular barrier function [43].

S1PR3 in cardiac ischemia-reperfusion

S1PR3 plays an important role in ischemia-reperfusion injury, exerting both direct protective action on the myocardium and a cardiosuppressive effect attributed to coronary vasoconstriction. The abundance of released S1P during ischemia-reperfusion may lead to competing influences on myocardial function via S1P3 receptor activation [44]. Elevated S1P levels, potentially induced by endogenous protective mechanisms, activate S1PR3 to mitigate myocardial defects and promote heart repair.

HDL-S1P binding to downstream S1PR3 receptors contributes to cardioprotection during ischemia-reperfusion, with S1PR3 activating the NO-dependent pathway [33]. Study has indicated that in mice lacking both S1PR2 and S1PR3 genes, the deletion of these receptors hinders Akt pathway activation, thereby inhibiting the damage-related extracellular signal-regulated kinase, c-Jun N-terminal kinase, p38MAPK pathways [45]. S1PR3, coupled to G12/13, activates downstream RhoA and Protein kinase D, further enhancing cardiac protection [27]. Additionally, during myocardial ischemia reperfusion, joint activation of S1PR2 and S1PR3 phosphorylates connexin 43 at S368, partially inhibiting cell-to-cell transmission of death signals and reducing cardiomyocyte damage (**Table 1** and **Figure 1**) [30].

Elevated S1P levels, triggered by endogenous protective mechanisms, activate S1PR3, alleviating myocardial defects and promoting heart repair. ECs promote vascular relaxation via S1P-S1PR1/S1PR3 signaling, while VSMCs mediate vasoconstriction under S1P-S1PR2/S1PR3 mediation [26]. FTY720 has been reported as a cardio-protective agent, alleviating either tachyarrhythmia or bradyarrhythmia induced by cardiac ischemia-reperfusion injuries [46].

In conclusion, S1PR3 has clinical research significance in ischemia-reperfusion injury. VPC01091, provides a similar protective effect to FTY720 on pulmonary ischemia-reperfusion injury, such as effectively protecting endothelial barrier function. The antagonistic activity of S1PR3 may not limit therapeutic potential, suggesting that VPC01091 may have therapeutic effects on cardiac ischemia-reperfusion by mediating S1PR3 [47].

S1PR3 in atherosclerosis

Disrupted lipid metabolism and inflammatory reactions contribute to elevated S1PR3 levels in atherosclerosis, further promoting inflammatory reaction and apoptosis to aggravate the damage of artery wall.

EC dysfunction stands as a key factor in atherosclerosis. S1P plays a crucial role in the maintenance of vascular integrity and the regulation of atherogenesis through the rearrangement of endothelial integrins [48]. S1PR3 regulates endothelial binding, uptake, and transport of HDL and low-density lipoproteins in an antagonistic manner. It influences the pathogenesis of atherosclerosis by inhibiting the trans endothelial transport of atherosclerotic low-density lipoproteins and promoting the trans endothelial transport of potentially anti atherosclerotic HDL [49]. It is currently believed that HDL-S1P in plasma initiates the coupling of S1PR3 with Gi protein to activate downstream pathways such as Rho/ROCK, PI3K/Akt and p38MAPK, which facilitate EC migration and inhibit atherosclerosis progression [34, 35].

Furthermore, HDL-S1P-mediated downstream S1PR3/STAT3 (Germline signal transducer and activator of transcription 3)/Survivin pathway can inhibit apoptosis induced by macrophage recruitment, thereby attenuating atherosclerosis (**Table 1** and **Figure 1**) [36]. S1P can be released from macrophages through ATP-binding cassette transporter A1, and regulate cholesterol efflux in a positive S1PR3 dependent feedback manner, thus hindering atherosclerosis [50]. In the bone marrow mosaicism model, S1PR3 deficiency reduces monocytes/macrophage recruitment but increases smooth muscle cell content at the lesion site [37, 38]. Existing studies have shown that 22(R)-hydroxycholesterol stimulates S1PR3, promoting the excretion of macrophage cholesterol into apolipoprotein A-I [51]. Hence, exhibits a dual role in atherosclerosis, both protective and modulating plaque composition.

Some anti-angiogenic effects of FTY720 involve blocking S1PRs implicated in recruitment of mural cells during angiogenesis. Combined inhibition of PDGFR and S1PR1/3 abolishes the network formation of VSMCs, making it a good candidate for anti-atherosclerosis treatment [52].

S1PR3 and cardiac fibrosis

Stimulation of S1PR3 in cardiac fibrosis escalates its expression and activity, promoting inflammatory response and cell apoptosis, thereby exacerbating the process of myocardial fibrosis. S1PR3 activates multiple pathways to promote this process.

S1P is highly expressed in fibroblasts and car-

diomyocytes, modulating them via paracrine mechanisms [43]. Cardiac fibroblasts endogenously express S1PR1, S1PR2, and S1PR3. Transgenic overexpression of SphK1 in mice leads to interstitial cardiac fibrosis mediated by S1PR3. Additionally, activation of S1PR3 coupled with Gq and G12/13 may also contribute to cardiac fibrosis [53]. The S1P/S1PR3/TGF-β/Smad3 pathway can orchestrates diverse downstream effects, including trans-activation of Smad3 phosphorylation, enhanced ROS production, reduced IL-1 and collagen fiber secretion, facilitated fibroblasts migration, and ultimately promotes cardiac fibrosis. Additionally, S1PR3 can activate Rho GTPase, promote ROS production and participate in the process of myocardial fibrosis, while S1PR3 deletion diminishes cardiac fibrosis [39]. Studies have revealed that S1P/S1PR3-mediated activation of the SUR2/Kir6.1 pathway in ventricular fibroblasts curbs IL-1 and collagen secretion, or enhances fibroblast migration, thereby mitigating fibrosis (**Table 1** and **Figure 1**) [41]. FTY-720 alleviates existing cardiac hypertrophy/fibrosis by negatively regulating NFAT (nuclear factor of activated T cells) activity in cardiomyocytes [54].

The advances in translational studies of S1PR3 for treating cardiovascular diseases

Reportedly, various regulators, including Fingolimod, VPC23019a, VPC01091, VPC44116, CYM5541, SPM242, exhibit affinity with S1PR3 [55]. While the regulatory effects of Fingolimod on S1PR3 have been explored in clinical phase I and II trials for cardiovascular disease, the impacts of other modulators remain to be fully elucidated.

FTY720 is a neural sphingosine 1-phosphate receptor modulator. It is the first S1PR modulator approved for the disease treatment [17]. Studies suggest that FTY720 may serve as a functional antagonist of S1PR3 to maintain a balance between angiogenesis and microvascular barrier function [43]. It mitigates tachycardia or bradycardia caused by myocardial ischemia-reperfusion injury by regulating S1PR3 [56]. Additionally, FTY720 exhibits anti-angiogenic effects by blocking S1PR involvement in mural cell recruitment during angiogenesis. The combined inhibition of PDGFR and S1PR1/3 completely eliminated the network forming ability of VSMCs, making it a good candidate for anti-atherosclerosis treatment [52]. FTY720 can also alleviate existing myocardial hypertrophy/fibrosis by negatively regulating the NFAT activity of myocardial cells [54].

Through chemical and biological assays, VPC01091 has been identified as an antagonist to S1PR3 [57]. VPC01091 provides a similar protective effect to FTY720 on pulmonary ischemia-reperfusion injury, such as effectively protecting endothelial barrier function. Importantly, the antagonistic activity of S1PR3 receptor may not limit therapeutic potential, suggesting that VPC01091 may have therapeutic promise for cardiac ischemia-reperfusion by mediating S1PR3 [47].

S1PR3 and perioperative period

Studies have shown that the measurement of circulating S1P can be used to predict the severity of inflammation caused by cardiac surgery, ICU hospitalization time, and general clinical outcomes [58]. Scholars have obtained S1PR3 related molecular features of 18 genes, in which many important immune pathways regulating the progression of sepsis have been enriched [59]. S1P lyase inhibition and S1PR3 stimulation can treat sepsis in mice [60]. Thrombin generated in the lymphatic compartment perturbs DCs to promote systemic inflammation and disseminated intravascular coagulation in severe sepsis. Signaling-selective aPC variants and selective modulators of the S1P receptor system attenuate sepsis lethality [61].

Conclusion

S1PR3, as a type of G protein coupled receptor in the body, exerts significant influence over a spectrum of pathological and physiological processes encompassing inflammation, cardiovascular function, oncogenesis, and neurological regulation. S1PR3 is expression varies across different tissues and cell types, being notably prevalent in EC, VSMC, glial cells, and lymphocytes. In the realm of cardiovascular diseases, including cardiac ischemia/reperfusion injury, atherosclerosis, and cardiac fibrosis, S1PR3 emerges as a key regulator, although further comprehensive research is warranted in this domain.

At present, modulators of S1PR3 like Fingolimod, VPC23019a, and VPC01091 are also widely used in clinical practice. S1PR3 also plays a crucial role during the perioperative period. The research on S1PR3 in cardiovascular disease continues to evolve. As a potential target for the treatment of cardiovascular diseases, S1PR3 holds the potential to significantly shape future treatment paradigms in this arena.

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study; Kecheng Zhai, Hui Su, and Renke Sun contributed to the literature and collection of materials; Yangmengna Gao and Ran Yuan contributed to material analysis and manuscript writing; Yangmengna Gao and Kecheng Zhai reviewed and refined the manuscript.

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